

APPLICATION FOR UNITED STATES PATENT

**LIQUID POLYMER COMPOSITION FOR PREVENTION AND
TREATMENT OF ORAL CAVITY DISEASES**

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FIELD OF THE INVENTION

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The present invention relates to a pharmaceutical composition for treating diseases of the mouth, in particular periodontal diseases.

BACKGROUND OF THE INVENTION

5 A periodontal disease is caused by a pathogenic microbial ecology established within the gingival sulcus which deepens to become a periodontal pocket. This microbial ecology, located deep within the periodontal pocket, differs greatly from that of the superficial oral environment by being more anaerobic, having a larger number of Gram negative organisms, and having a greater proportion of motile species.

10 Several factors prevent medicinal agents from diffusing when applied to the superficial periodontal tissues. Anatomically, the gum tissue is closely adapted to the neck of the teeth, mechanically restricting the diffusional pathway. In addition, a fluid termed gingival crevice fluid, which has the approximate composition of plasma, permeates the periodontal environment and is
15 continually produced by the diseased periodontal tissues at a rate of 10 to 100 microliters per hour. This fluid, emanating from the diseased pocket lining, creates a net outward flow, which further impedes the introduction of medications by superficially applied drug delivery devices.

20 These interferences are sufficiently effective to insulate the pocket environment to the extent that saliva does not penetrate, and topically applied medicinal agents have been found largely ineffectual in the treatment of established periodontitis. Although mouth rinses may be effective in the reduction of superficial gingivitis resulting from poor home care procedures, the
25 effective radius of action of these agents does not extend to the periodontal pocket.

Introduction of antibacterial agents in solution into the periodontal pocket is also ineffective due to the rapid clearance thereof, so that the duration of contact at
30 the active site is minimal. Conventional therapy for periodontal disease, as first enunciated by Pierre Fauchard in 1746 in his book entitled "The Surgeon Dentist, a

Treatise on Teeth", involves the mechanical removal of bacterial plaques and accumulations from the periodontal pocket at periodic intervals. This may include periodontal surgery to achieve access and to recontour damaged tissues. These procedures require a high degree of technical expertise from the practitioners of the art, are expensive, and often result in pain, extensive bleeding, and general local discomfort. Since these procedures provide, at best, only temporary reduction in bacterial populations, they must be repeated at regular intervals to be effective. As discussed by Lindhe and co-workers, in "Healing Following Surgical/Non-Surgical Treatment of Periodontal Disease, a clinical study" in Journal of Clinical Periodontology, vol. 9, pages 115-128, (1982), the frequency of repetition needed for optimal results may be as high as once every two weeks.

Methods for administering drugs for periodontal therapy have heretofore largely been concerned with superficial application. For example:

- 15 long-acting capsules or tablets held in the mouth (US 3,911,099);
 - buccal implants for releasing drugs into the saliva (US 4,020,558);
 - topically applied gels (US 3,679,360);
 - topically applied drug-containing bandages (US 3,339,546);
 - a drug containing plastic hardenable mass (US 3,964,164);
 - 20 – a medicated periodontal dressing (US 3,219,527);
 - a topical dressing composed of a finely divided particulate carrier and suspended medicinal agents (US 3,698,392);
 - a bandage for covering moist mucosal surfaces (US 3,339,546);
 - a microencapsulated liquid droplet formation for topical application to the gums of dogs and other animals (US 4,329,333);
 - 25 – and foam film devices containing medication (US 3,844,286).

In addition, several fibrous forms for superficial medication have been described, including:

- 30 – impregnated or drug-releasing forms of dental floss (US Pat. Nos. 3,417,179, 2,667,443, 2,748,781, 3,942,539);

- solid absorbable fibres of polyglycolic acid with medicates incorporated therein (US 3,991,766);
- and cellulose acetate hollow fibres (US 4,175,326).

5 Systemic antibiotic therapies for periodontal infections have also been used. In this instance, the objective is to eliminate or suppress any growth of specific pathogenic species. Systemic administration of antibiotics starts by selection of the antibiotic with appropriate antibacterial spectrum. Thus, for example, one might administer penicillin to eliminate Gram positive anaerobe
10 infections, metranidazole to eliminate Gram negative anaerobe infections, and tetracycline to eliminate actinobscillus infections. Actually, specific organisms sensitive to the relatively low concentrations of antibiotic achieved by this therapy (ca. 2-10 ug/ml) are selectively eliminated.

15 Owing to the low concentrations of antibiotic achieved by systemic administration and the relative high levels of bacterial resistance associated with periodontal pathogens, the clinical success of this therapy has been poor, as discussed by Genco in "Antibiotics in the Treatment of Human Periodontal Diseases", in G. Periodontology, vol. 52, pages 545-558 (1981). Thus, it appears
20 that none of the previously disclosed procedures has led to an acceptable system for delivering optimally effective levels of antibacterial substances to the site of periodontal disease activity.

EP0404558 describes the use of a therapeutic agent delivery device to be
25 placed within the periodontal pocket in such a manner that the diseased pocket regions come in intimate contact with it. The active agent is thus released at the site of disease, eliminating the variability inherent in long diffusional pathways associated with superficial or systemic treatments. The composition has a liquid methacrylic polymer, a therapeutic agent and a release adjusting agent. The polymer
30 retains the therapeutic agent, and the release adjusting agent progressively dissolves the polymer so that the therapeutic agent is slowly released. However, owing to the

presence of the release adjusting agent, biocompatibility may be reduced, in particular in presence on bone wounds, as well as allergic problems may arise. Moreover, the addition of an adhesive agent is suggested, since the polymeric film may not adhere to the surface to treat. Polyethylene glycols or dibutyl Phthalate are the preferred plasticizers; such agents play a role in enhancing the rate of degradation of the film and in improving its adherence. A further limit is that the release of the therapeutic agent can last not more than a few hours. In addition, it appears that delivery of optimal concentrations of any medicinal agent to disease sites within the periodontal pocket has not been addressed. The suggested liquid methacrylic polymer are: alcoholic solutions of Eudragit[®] RL (available from Rohm Speciality Acrylics) with Eudispert as release adjusting agent; Eudragit RS+RL in ratio 1/1 with Eudispert as release adjusting agent. Other release adjusting agents are cross-linking agents (such as glutaraldehyde, citric acid, lysine, aspartic acid, glutaric acid), polysaccharides (such as dextran), lipids (such as sodium docusate), polihydroxycompound (such as PEG, glycerol, propylene glycol), protein (such as Byco E or Byco C).

A similar approach is described in DE4125048, wherein Eudragit E is used that forms a polymeric film soluble in water. This way, a controlled release of a therapeutic agent is obtained by dissolution in saliva of the film. However, this mechanism does allow a release of the therapeutic agent in short periods such as a few hours.

Other similar approaches to this problem are described in:

- EP 140766, wherein a polymeric matrix such as ethylene vinyl acetate copolymer and other copolymers or fibres are used which are semi-permeable to a therapeutic agent. The copolymer is put into the periodontal pocket and then removed after a certain time, during which the therapeutic agent has been released. This system has the drawback that the polymeric matrix is semi permeable and not fully permeable. For this reason, it does not adhere to the pocket surface as a film and is used only as biocompatible physical vehicle for

the therapeutic agent. Moreover, the polymeric matrix has to be released after a certain time, and this requires a further surgery operation;

- US A3925895 describes a methacrylate polymer used for filling canal roots in which a medicament may be incorporated;
- 5 – US A 3956480 describes a treatment of teeth by sorbing onto the tooth surfaces a combination of a cationic germicide and an anionic polymer;
- US A 3846542 relates to an acrylic tooth-filling composition containing boric acid-releasing compound;
- EP A2 0264660 describes the use of a dental material for combating caries
10 and periodontosis.

SUMMARY OF THE INVENTION

It is therefore a feature of the present invention to provide a new composition for treating periodontal disease, by means of a therapeutic agent
15 delivery device placed within the periodontal pocket, such that release of the therapeutic agents occurs in the immediate vicinity of the disease process, without that a release adjusting agent or adhesive agent is present so that biocompatibility or allergic problems cannot arise.

20 It is another feature of the present invention to provide a new composition for treating periodontal disease by means of a therapeutic agent delivery device, wherein a slow release of a therapeutic agent is obtained lasting more than in the prior art, and up to 7-10 days.

25 It is another feature of the present invention to provide a new composition for protecting bacterial growth in the vicinity of buccal wounds, and also inside the cavity, such as after surgery like in a socket after dental extraction, after implants, cysts, gingival abscess, apicectomy, granuloma etc., wherein a mechanical protection on the wounds as well as a barrier to bacteria having is obtained at the
30 same time.

DESCRIPTION OF THE INVENTION

In a composition according to one exemplary embodiment of the invention for prevention and treatment of oral cavity diseases, a therapeutic agent
5 in a biocompatible polymeric material is provided, said therapeutic agent is soluble both in water and in alcohol, and that said biocompatible polymeric material is a liquid methacrylate copolymer selected from the group consisting of EUDRAGIT[®] RL, EUDRAGIT[®] RS, and a mixture thereof.

10 Preferably, said liquid methacrylate copolymer is a mixture of EUDRAGIT[®] RS 100 and EUDRAGIT[®] RL 100.

Preferably the polymer/s is/are provided as a liquid in an alcoholic solution, preferably about 96°C . When the polymer is spread on a surface, such
15 as by a little brush, the alcohol evaporates and the polymer forms a polymeric film on that surface.

Alternatively, the polymer/s are provided in a idroalcoholic solution. In this case, the mixture ethanol and water is 1-20% w/w of water. The presence of
20 this little amount of water is advantageous for enhancing the solubilisation of the therapeutic agent when the latter has not high solubility in alcohol, and on the other hand it has a good solubility in water. In this way the preparation of the composition by mixing the polimeric solution and the therapeutic agent (i.e., powder) is faster. Up to 20% of water both the polimeric solution and the final
25 liquid composition remain as a clear solution, i.e., without precipitation of the polymer/s.

Moreover, the liquid polymer can be injected directly into the periodontal pocket, forming a film in situ and releasing the active agent
30 according to the invention in a controlled manner over a desired period of time.

Chemically, EUDRAGIT RS and RL are copolymers of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. The polymers are described in USP/NF as "ammonium methacrylate copolymer, type A" (EUDRAGIT[®]RL) and "type B" (EUDRAGIT[®]RS).

A first advantage of the composition according to the invention is that if a therapeutic agent that is soluble both in water and in alcohol is used, within the biocompatible polymeric comprising EUDRAGIT[®]RL or EUDRAGIT[®]RS or a mixture thereof, the polymeric film surprisingly adheres to the surfaces and no adhesive additives are necessary. This increases substantially biocompatibility with respect to the prior art, since no adhesive material is necessary, that is instead required in EP0404558. Moreover, this adhesivity does not require that a large amount of polymer is used up to filling the periodontal pockets or other cavities, thus avoiding the need of removing the device later. This allows the cavity to collapse spontaneously and the film to be dissolved naturally in the mouth environment.

A main advantage of the present invention that enhances biocompatibility is that no release adjusting agent is necessary, that is instead required in EP0404558. This result is given by the synergic combination of biocompatible polymeric material, i.e., comprising EUDRAGIT[®]RL or EUDRAGIT[®]RS or a mixture thereof, and therapeutic agent that is soluble both in water and in alcohol.

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More precisely, the film of biocompatible polymeric material is not soluble into water and then it is durable up to a normal consumption within the mouth environment, several days to several weeks, depending on the quantity. If in the film a therapeutic agent is present that is soluble in alcohol but not in water, when water present in the mouth tissues permeates through the film, the

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therapeutic agent is not released. On the other hand, if a therapeutic agent is not soluble in alcohol, it cannot be accepted within the polymer alcoholic solution.

Therefore, according to the invention, if in the film of biocompatible polymeric material a therapeutic agent is present that is soluble both in alcohol and in water, when water present in the mouth tissues permeates through the polymeric material, the therapeutic agent is released. The release rate is dependent from the permeability to water of the polymeric material. Mixtures may be obtained from which the therapeutic agent will diffuse at a controlled rate over selected periods of time.

More precisely, by proper selection of the two polymeric material EUDRAGIT RS and RL, a precise release rate is obtained. In fact, by varying the ratio RS/RL the hydrophilic property varies accordingly. In particular, if RL is increased, the release rate of the therapeutic agent is increased. Preferably, the ratio RS/RL is comprised between 1.5:1 and 3:1, so that the release of the therapeutic agent lasts up to 7-10 days. The preferred ratio RS/RL is 2:1.

The therapeutic agent that is soluble both in water and in alcohol is preferably chosen among:

Antibacterial Agents – chlorexidine acetate, thimerosal, cetylpyridinio chloride, benzalkonium chloride, cetrimide, benzethonium chloride;

Antibiotics - piperacillin sodium, carbenicillin sodium, carindacillin sodium, chloramphenicol sodium succinate, clindamycin palmitate hydrochloride, cloxacillin sodium, erythromycin gluceptate and lactobionate, flucloxacillin sodium, lincomycin hydrochloride, nafcillin sodium, tetracycline hydrochloride, minocycline;

Dentinal desensitizing agents - strontium chloride, zinc chloride, calcium chloride, magnesium chloride stannous chloride, potassium sorbate;

Antivirals - acyclovir, idoxouridine, amantadine;

and mixtures thereof.

A useful adjuvant procedure to the surgical treatment to prevent or to treat infections of the above mentioned diseases is to put into the cavity a sponge of collagen, alginate, hyaluronate with liquid polymer.

5 This invention is not limited to the use of the above agents alone. A wide variety of therapeutic agents may be used in the invention, which can be delivered in this way and are potentially effective for periodontal therapy. It is recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus,
10 for example, an antibacterial and an anti-inflammatory agent may be combined in a single delivery system to provide combined effectiveness.

 A further advantage deriving from the use of this new composition according to the invention is the following. Since the volume of distribution is
15 limited to the total volume of gingival crevice fluid produced within the periodontal pocket, relatively high concentrations of therapeutic agent are developed in the pocket. However, the overall amount of therapeutic agent required under these conditions is low, typically a few milligrams. This small amount greatly reduces the effect of the therapeutic agent same at distal sites
20 within the body, thereby greatly decreasing the potential for systemic side effects. By establishing local concentrations of an antibacterial agent sufficient to inhibit growth of all bacteria within the pocket, development of drug resistant strains is minimized. The potential for encouraging the development of drug-resistant pathogens is further minimized by the relatively short duration to
25 achieve the desired effect, typically about three to ten days. By this procedure, the therapeutic agent delivery according to the invention, corresponding to a few milligrams of therapeutic agent, gives effects greater than those expected by the same drug used at much higher dosage by other routes of distribution. This principle results in an unexpectedly high degree of effectiveness from the
30 comparatively small amount of drug utilized. The use of a periodontal or other

mechanical retaining and/or diffusion-limiting device further enhances therapeutic effectiveness.

EXAMPLES

5 Not limitative examples of the present invention are the following:

EXAMPLE 1

Solution

Eudragit RL 100 4.5% (w/w)

Eudragit RS 100 7.5% (w/w)

10 Ethanol 96% q.s. 100 g

Powder

Piperacillin sodium 10% (w/w)

EXAMPLE 2

Solution

15 Eudragit RL 100 4.5% (w/w)

Eudragit RS 100 7.5% (w/w)

Purified water 18% (w/w)

Ethanol 96% q.s. 100 g

Powder

20 Piperacillin sodium 10% (w/w)

EXAMPLE 3

Solution

Eudragit RL 100 4.5% (w/w)

Eudragit RS 100 7.5% (w/w)

25 Ethanol 96% q.s. 100 g

Powder

Chloramphenicol sodium succinate 10% (w/w)

EXAMPLE 4

Solution

Eudragit RL 100 4.5% (w/w)

5 Eudragit RS 100 7.5% (w/w)

Ethanol 96% q.s. 100 g

Powder

Clindamycin palmitate 10% (w/w)

EXAMPLE 5

10 Eudragit RL100 4.5% (w/w)

Eudragit RS100 7.5% (w/w)

Cetrimide 0.5%(w/w)

Chlorexidine acetate 0.2% (w/w)

Ethanol 96% q.s. 100 g

15 EXAMPLE 6

Solution A

Potassium fluoride 5% (w/w)

Dibasic potassium phosphate 10% (w/w)

Purified water q.s. 100 g

20 Solution B

Calcium chloride 5% (w/w)

Zinc chloride 7.5% (w/w)

Eudragit RS100 6% (w/w)

Ethanol 96° C q.s. 100 g

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According to Example 6, a dental composition for treatment of dentinal hypersensitivity may be obtained as two distinct solutions as a liquid or gel mixed topically on the exposed dentin. The first solution (A) comprises two soluble potassium salts, whereas the second solution (B) comprises a calcium salt and a
30 soluble zinc salt. After mixing on the dentinal surface the solution A and B, a soluble

potassium chloride is obtained that has desensitising properties, as well as zinc and calcium insoluble salts. The insoluble salts obliterate the dentinal tubules closing within it also the potassium chloride. An alcoholic solution B according to the invention, has the following advantages: solution B can be applied quickly owing to
 5 quick evaporation of the alcohol; solution B penetrates better in the tubules; Eudragit[®] RS100 is surprisingly adhesive owing to the presence of water soluble therapeutic agents; the reaction occurs within the film with a consequent stabilisation of the resulting salts. The film forms a further mechanical block to the dentinal tubules and there is a slow release of potassium chloride according to the principles of the
 10 invention. The use of zinc allows the precipitation of proteins within the tubules, thus limiting liquid permeation within tubules that causes hypersensitivity.

EXAMPLE 7

Solution A

15 Potassium fluoride 15% (w/w)
 Purified water q.s. 100 ml

Solution B

Zinc chloride 3% (w/w)
 Strontium chloride 8% (w/w)
 20 Eudragit RS100 4% (w/w)
 Purified water 17% (w/w)
 Ethanol 96% q.s. 100 g

Also this is a dental composition like Example 5 with the difference that strontium insoluble salts are obtained instead of calcium salts. Strontium has
 25 known desensitising properties.

EXAMPLE 8

Acyclovir 3% (w/w)
 Eudragit RL100 4.5% (w/w)
 30 Eudragit RS100 7.5% (w/w)
 Transcutol 10% (w/w)

Ethanol 96% q.s. 100 g

This composition is used for treating diseases caused by Herpes Labialis.

5 The foregoing description in the form of examples will so fully reveal the invention according to the conceptual point of view, so that others, by applying current knowledge, will be able to modify and/or adapt for various applications such examples without further research and without parting from the invention, and it is therefore to be understood that such adaptations and modifications will have to be
10 considered as equivalents to the specific examples. The means and the materials to realise the different functions described herein could have a different nature without, for this reason, departing from the field of the invention. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation.

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All patents, patent applications, and publications referred herein are incorporated by reference by their entirety.